The Preterm Prediction Study: The Value of New vs Standard Risk Factors in Predicting Early and All Spontaneous Preterm Births

ABSTRACT

Objective. This study was undertaken to determine the relationship between fetal fibronectin, short cervix, bacterial vaginosis, other traditional risk factors, and spontaneous preterm birth.

Methods. From 1992 through 1994, 2929 women were screened at the gestational age of 22 to 24 weeks.

Results. The odds ratios for spontaneous preterm birth were highest for fetal fibronectin, followed by a short cervix and history of preterm birth. These factors, as well as bacterial vaginosis, were more strongly associated with early than with late spontaneous preterm birth. Bacterial vaginosis was more common—and a stronger predictor of spontaneous preterm birth—in Black women, while body mass index less than 19.8 was a stronger predictor in non-Black women. This analysis suggests a pathway leading from Black race through bacterial vaginosis and fetal fibronectin to spontaneous preterm birth. Prior preterm birth is associated with spontaneous preterm birth through a short cervix.

Conclusions. Fetal fibronectin and a short cervix are stronger predictors of spontaneous preterm birth than traditional risk factors. Bacterial vaginosis was found more often in Black than in non-Black women and accounted for 40% of the attributable risk for spontaneous preterm birth at less than 32 weeks. (*Am J Public Health.* 1998;88:233–238)

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Introduction

Numerous risk factors and tests are purported to predict spontaneous preterm birth.[1–10] The best predictor has been a prior spontaneous preterm birth, followed first by Black race and then by some measure of maternal thinness, such as the body mass index. Recently, we reported on three tests that were significantly associated with spontaneous preterm birth: bacterial vaginosis,[11–14] fetal fibronectin in the vagina or cervix,[15–19] and short cervical length[20] as determined by ultrasound. Because of the strength of these risk factors, we wanted to determine how each acted independently and together to predict spontaneous preterm birth.

Methods

This study was carried out by the National Institute of Child Health and Human Development Maternal Fetal Medicine Network from 1992 to 1994. At each of 10 centers, women were selected to reflect the population by race and parity. Research nurses and sonographers collected the data at specially designed study visits. The study was approved by each institutional review board, and each participant provided informed consent.

Prior to the study, the primary outcome was defined as spontaneous preterm birth (following premature rupture of membranes or spontaneous labor) at less than 35 weeks' gestational age. Sample size was based on the precision of the odds ratio (OR). Assuming a proportion of at least 5% testing positive for a given screening test, a 3.5% rate of spontaneous preterm birth at less than 35 weeks, and an odds ratio of at least 2, a sample size of 3000 women was chosen to give a lower 95% confidence interval (CI) of greater than 1. Initially, 3073 women enrolled in the study. Of these, 73 gave consent but were excluded because enrollment occurred outside the required gestational age window, and 71 were lost to follow-up. This left 2929 pregnancies available for analysis.

Participants were identified at or prior to 24 weeks' gestation. Before enrollment, each woman had an ultrasound examination for dating and for ruling out placenta previa and major anomalies. Gestational age was

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based on the last menstrual period if the last menstrual period and the earliest ultrasound biparietal diameter agreed within 10 days. If they did not, the biparietal diameter was used to define gestational age. Women with multiple gestation, cervical cerclage, placenta previa, or major fetal anomaly were deemed ineligible. After enrollment, only data related to fetal death, prolapsed membranes, cervical dilation of at least 2 cm in primigravidas and at least 3 cm in multigravidas, polyhydramnios, oligohydramnios, and regular contractions were made available to the women's physicians.

Data collected included prepregnancy weight and height, pregnancy history, cervical ultrasound, and cervical and vaginal sampling for bacterial vaginosis and fetal fibronectin. Body mass index in kilograms per square meter was derived from prepregnancy weight and measured height. Bleeding after 13 weeks and the presence of contractions in the prior week were based on self-report. "Pelvic infection" included chlamydia, gonorrhea, syphilis, herpes, yeast, or trichomonas, as determined by chart review or a reported history of pelvic inflammatory disease. The study visit occurred at 22 to 24 weeks and a subsequent visit was scheduled 2 weeks later for fetal fibronectin testing based on reports of improved efficacy for predicting preterm birth with repeated testing.[15–18]

Samples for fetal fibronectin were obtained from the posterior vaginal fornix and cervix with a Dacron swab[15–18] and were analyzed by Adeza Biomedical Company in Sunnyvale, California. A positive test for fetal fibronectin was defined as any value of 50 ng/mL or above. Bacterial vaginosis was defined by a Gram's stain using the criteria of Nugent et al.[21] Cervical length measurement methodology has been described previously[20]: a cervical length of 25 mm represented the 10th percentile and, using receiver operator characteristic curves, was the best cutoff for defining a "short cervix."[20]

Statistical analysis was performed with the use of the SAS system. For univariate analyses, chi-square tests were used, and odds ratios, relative risks (RRs), and 95% confidence intervals were calculated. Population attributable risk was calculated by the method of Kleinbaum et al.[22] Final logistic regression models were derived by backward elimination and checked by forward selection.

Results

The population was 63% Black and 37% non-Black, had a mean age of 23.7 ± 5.5 years, and had 11.9 ± 1.9 years of education; 28% were married, 42% were nulliparous, 31% smoked, and 54% earned less than $9600 per year. Characteristics not associated with spontaneous preterm birth at less than 32 weeks, less than 35 weeks, or less than 37 weeks included maternal age below 18 years, educational level, urinary tract infection, most medical complications, smoking, drug or alcohol use, pelvic pressure and diarrhea, and previous induced or spontaneous abortions. Table 1 shows the nine characteristics associated with spontaneous preterm birth at each designated gestational age and the number of women with and prevalence of each characteristic. It also presents the relative risks (and 95% CIs) for spontaneous preterm birth of women with the characteristics compared with the reference group.

The incidence of spontaneous preterm birth at less than 32 weeks ranged from about 1.0% for women in the lower risk groups to 12.9% for women with fetal fibronectin. The three strongest predictors of spontaneous preterm birth at this time were fetal fibronectin, a cervix not exceeding 25 mm, and prior spontaneous preterm birth. Other significant predictors included body mass index below 19.8, vaginal bleeding, and bacterial vaginosis. Characteristics significantly associated with spontaneous preterm birth at less than 35 weeks included body mass index of up to 26, prior spontaneous preterm birth, contractions, vaginal bleeding, fetal fibronectin, and a short cervix. While nearly every factor was significantly associated with spontaneous preterm birth at less than 37 weeks, fetal fibronectin, a short cervix, and prior spontaneous preterm birth were once again the strongest predictors.

Table 2 shows the prevalence and the population attributable risk for spontaneous preterm birth associated with each risk factor in Black and non-Black women at the three gestational ages. We emphasize that the population attributable risk represents the hypothetical reduction in the incidence of spontaneous preterm birth if the factor were eliminated.

At less than 32 weeks, 7% of Black women and 6% of non-Black women tested positive for fetal fibronectin. In both groups, fetal fibronectin was associated with the highest population attributable risk for spontaneous preterm birth (43% and 55%, respectively). A short cervix, which was present in 10% and 8% of Black and non-Black women, respectively, was also associated with a high population attributable risk for spontaneous preterm birth (43% and 31%, respectively). A prior spontaneous preterm birth was present in 14% of Black women and 10% of non-Black women and was associated with population attributable risks of 39% and 21%, respectively, for this outcome. Bacterial vaginosis was present in 29% of Black women but in only 15% of non-Black women. In Black women, bacterial vaginosis had a population attributable risk for spontaneous preterm birth of 40%, but it had no population attributable risk in non-Black women. A low body mass index was equally common in Black and non-Black women, but only in non-Black women was it associated with a high population attributable risk for spontaneous preterm birth (46% vs 2%). Vaginal bleeding was present in about 9% of both non-Black and Black women, but only in non-Black women was the population attributable risk for spontaneous preterm birth elevated. The other 2 risk factors were present in 16% to 34% of women but were associated with relatively low attributable risks.

The population attributable risks associated with each of the risk factors for spontaneous preterm birth at less than 35 weeks and less than 37 weeks are also presented in Table 2. For most risk factors, the population attributable risk declined as the gestational age window for spontaneous preterm birth expanded.

Table 3 shows the risk of spontaneous preterm birth in association with combinations of the three strongest risk factors. For nulliparas and multiparas, the risks of spontaneous preterm birth associated with the individual risk factors were approximately equal; the presence of 2 or 3 risk factors in combination substantially increased those risks. If fetal fibronectin was one of the factors present, the risk was higher than if fetal fibronectin was absent. If any 2 factors were present, the overall risk of spontaneous preterm birth at less than 32 weeks was increased about 35-fold, and if each of the 3 factors was present, that risk was increased 100-fold.

Table 4 shows the results of the final regression models used to predict spontaneous preterm birth. For spontaneous preterm birth at under 32 weeks in nulliparas, both fetal fibronectin and short cervical length remained powerful predictors. In multiparas, a positive finding of fetal fibronectin remained the strongest risk factor, but short cervical length, bacterial vaginosis, vaginal bleeding, and prior spontaneous preterm birth were each significant predictors. As the gestational age window expanded to include later spontaneous preterm birth, a greater number of factors became significant predictors; for the strongest predictors, however, the odds

TABLE 1—The Relationship between Maternal Characteristics and Spontaneous Preterm Birth (SPB) at Various Gestational Ages

		SPB < 32 weeks		SPB < 35 Weeks		SPB < 37 Weeks	
	No.	Percent	RR (95% CI)	Percent	RR (95% CI)	Percent	RR (95% CI)
Race							
Black	1838	2.0	1.5 (0.8, 2.8)	4.8	1.4 (0.96, 2.0)	11.8	1.5 (1.2, 1.9)
Non-Black	1091	1.3		3.5		7.9	
Body mass index							
<19.8	550	2.7	2.6 (1.1, 6.2)	7.1	3.0 (1.7, 5.1)	16.6	2.5 (1.8, 3.5)
19.8–26.0	1251	1.8	1.7 (0.7, 3.9)	4.9	2.1 (1.2, 3.5)	10.3	1.6 (1.1, 2.2)
26.1–29.0	363	1.4	1.3 (0.4, 4.1)	2.2	0.9 (0.4, 2.1)	7.4	1.1 (0.7, 1.8)
>29	674	1.0		2.4		6.3	
Previous SPB in multiparas							
Present	363	5.8	7.1 (3.8, 13.2)	15.2	6.4 (4.4, 9.2)	23.4	2.7 (2.1, 3.4)
Absent	1348	0.8		2.4		8.8	
Primiparas	1218	1.5		3.3		8.1	
Contractions							
Yes	514	2.3	1.5 (0.8, 2.8)	7.8	2.2 (1.5, 3.1)	16.2	1.8 (1.4, 2.3)
No	2415	1.6		3.6		9.1	
Vaginal bleeding							
Yes	275	4.0	2.7 (1.4, 5.1)	7.6	1.9 (1.2, 3.0)	14.9	1.5 (1.1, 2.1)
No	2653	1.5		4.0		9.8	
Pelvic Infection							
Yes	830	1.8	1.1 (0.6, 2.0)	4.8	1.2 (0.8, 1.7)	12.2	1.3 (1.0, 1.6)
No	2099	1.7		4.1		9.6	
Bacterial Vaginosis							
Positive	678	3.2	2.7 (1.6, 4.6)	5.5	1.4 (0.9, 2.0)	12.3	1.3 (0.98, 1.6)
Negative	2222	1.2		4.0		9.8	
Fetal fibronectin							
Positive	194	12.9	14.1 (9.3, 21.4)	21.1	6.7 (4.9, 9.2)	29.4	3.3 (2.5, 4.2)
Negative	2734	0.9		3.2		9.0	
Cervical length							
≤25 mm	264	8.3	7.7 (4.5, 13.4)	17.8	6.5 (4.5, 9.3)	26.9	3.5 (2.7, 4.6)
26–35 mm	1262	0.9	0.9 (0.4, 1.9)	3.3	1.2 (0.8, 1.8)	9.8	1.3 (1.0, 1.7)
>35 mm	1389	1.1		2.7		7.6	

Notes. RR = Relative risk; CI = confidence interval.

ratios for spontaneous preterm birth tended to decrease.

In addition to predicting spontaneous preterm birth at less than a specific gestational age threshold—that is, at less than 32 weeks, at less than 35 weeks, or at less than 37 weeks, as shown in Table 4—one could also predict delivery within a specific gestational age window, such as 24 to 31 weeks, 32 to 34 weeks, or 35 to 36 weeks. In this study, 1.7% of the women delivered at 24 to 31 weeks, 2.6% at 32 to 34 weeks, and 6.0% at 35 to 36 weeks. The relationship of the risk factors to spontaneous preterm birth at 24 to 31 weeks is shown in Table 4. In analyses of the relationship between these same risk factors and spontaneous preterm birth at 32 to 34 weeks and at 35 to 36 weeks (data not shown), fetal fibronectin remained a significant predictor at the earlier age (OR 2.2; CI = 1.5, 4.3) but not at the later one (OR 1.3; CI = 0.8, 2.3). Short cervix also remained a significant predictor of spontaneous preterm birth at 32 to 34 weeks (OR 4.2; CI = 2.4, 7.1), but not at 35 to 36 weeks (OR 1.4; CI = 0.9, 2.3). Prior spontaneous preterm birth also was a strong predictor at 32 to 34 weeks (OR 4.8; CI = 2.9, 7.8) but not at 35 to 36 weeks (OR 1.2; CI = 0.8, 1.9). Of the other risk factors, the only significant predictor at 32 to 34 weeks was contractions (OR 2.2; CI = 1.3, 3.6) and at 35 to 36 weeks, body mass index (OR 1.9; CI = 1.4, 2.7) and Black race (OR 1.5; CI = 1.0, 2.1).

We also evaluated how the various factors were associated with one another. In this analysis, most odds ratios were less than 2 or were not significant in both nulliparas and multiparas. However, consistent, powerful associations in nulliparas and multiparas included the relationship between Black race and bacterial vaginosis (OR = 2.3 and 2.4, respectively), between Black race and pelvic infections (OR = 1.9 and 2.4, respectively), and between short cervix and fetal fibronectin (OR = 3.1 and 3.5, respectively). In multiparas, prior spontaneous preterm birth was most strongly associated with a short cervix (OR = 3.1).

Discussion

Demographic data, laboratory tests, and physical examination data have been studied as predictors of spontaneous preterm birth.[1–10] Unfortunately, the sensitivity and/or specificity of these tests is low, and their utility is not great. In addition, it is not clear if any available preventive measure or treatment for spontaneous preterm birth is effective,[23] other than the treatment of bacterial vaginosis in high-risk women.[13]

We evaluated the relationship between many potential factors and spontaneous preterm birth but found relatively few significant associations. Those we found included Black race, low body mass index, vaginal bleeding, contractions, pelvic infection, bacterial vaginosis, prior spontaneous

TABLE 2—Prevalence and Population Attributable Risk (PAR) of 8 Maternal Characteristics for Spontaneous Preterm Birth (SPB) at Various Gestational Ages in Black and Non-Black Women

	SPB < 32 Weeks			
	Black 36/1838 = 2.0%		Non-Black 14/1091 = 1.3%	
	Prevalence, %	PAR, %	Prevalence, %	PAR, %
Fetal fibronectin	7.2	43.3	5.7	54.7
Cervix length ≤ 25 mm	10.0	43.0	7.5	30.7
Previous SPB	13.8	38.7	10.0	20.6
Bacterial vaginosis	28.6	39.9	14.6	—
Body mass index < 19.8	18.3	2.0	21.2	45.6
Vaginal bleeding	9.5	8.0	9.3	29.1
Contractions	16.5	6.9	19.3	11.4
Pelvic infection	33.8	3.5	19.2	—
	SPB < 35 weeks			
	Black 89/1838 = 4.8%		Non-Black 38/1091 = 3.5%	
	Prevalence, %	PAR, %	Prevalence, %	PAR, %
Fetal fibronectin	7.2	28.6	5.7	24.7
Cervix length ≤ 25 mm	10.0	33.1	7.5	26.1
Previous SPB	13.8	38.7	10.0	26.9
Bacterial vaginosis	28.6	12.5	14.6	4.8
Body mass index <19.8	18.3	12.4	21.2	22.5
Vaginal bleeding	9.5	8.2	9.3	7.2
Contractions	16.5	19.2	19.3	11.9
Pelvic infection	33.8	—	19.2	12.1
	SPB < 37 Weeks			
	Black 216/1838 = 11.8%		Non-Black 86/1091 = 7.0%	
	Prevalence, %	PAR, %	Prevalence, %	PAR, %
Fetal fibronectin	7.2	13.7	5.7	11.2
Cervix length ≤ 25 mm	10.0	16.3	7.5	14.6
Previous SPB	13.8	18.9	10.0	14.7
Bacterial vaginosis	28.6	7.6	14.6	—
Body mass index <19.8	18.3	13.6	21.2	19.0
Vaginal bleeding	9.5	4.4	9.3	8.0
Contractions	16.5	14.6	19.3	6.3
Pelvic infection	33.8	4.2	19.2	3.5

preterm birth, fetal fibronectin, and short cervix, the last three being the strongest predictors. The importance of the other factors varied depending on the type of analysis and the spontaneous preterm birth/gestational age window.

Prior spontaneous preterm birth, short cervix, and fetal fibronectin were each present in a relatively small proportion of the population. The population attributable risk for spontaneous preterm birth associated with each of these risk factors was high, so if an effective intervention were associated with any of these characteristics, it would be possible to target a relatively small portion of the pregnant population. We also emphasize that these 3 risk factors, as well as bacterial vaginosis, each had stronger associations with early rather than with late spontaneous preterm birth.

Examination of the association between factors yields additional insights. At 24 to 26 weeks, Black race predicted bacterial vaginosis, which was significantly associated with fetal fibronectin. Prior spontaneous preterm birth was most strongly associated with a short cervix. A strong relationship was also present between a short cervix and fetal fibronectin. However, in the entire population, of the 193 women who tested positive for fetal fibronectin, and of the 264 women with a short cervix, only 43 had both risk factors. Similarly, of the 264 women with a short cervix, only 58 had prior spontaneous preterm birth. Only 10 women had all three risk factors. The overlap, therefore, was relatively small. We cannot determine from these data if the overlap between a short cervix and fetal fibronectin increases closer to delivery, but we speculate that as delivery approaches, women would be more likely to develop both risk factors.

Among the three strongest predictors of spontaneous preterm birth, the associations with spontaneous preterm birth were more than additive. Only 0.5% of women with no risk factors had spontaneous preterm birth at less than 32 weeks. If a prior spontaneous preterm birth, short cervix, or fetal fibronectin was present, the risk of spontaneous preterm birth at this time rose to 2 to 3%. If 2 of these risk factors were present, the risk rose to 8 to 27%. If all three were present, the risk rose to

TABLE 3—Risk of Spontaneous Preterm Birth at Various Gestational Ages with Various Combinations of Risk Factors in Nulliparas and Multiparas

	Nulliparas				Multiparas			
Risk Factor	n	<32 Weeks, %	<35 Weeks, %	<37 Weeks, %	n	<32 Weeks, %	<35 Weeks, %	<37 Weeks, %
All negative	1033	0.6	1.7	6.0	1190	0.5	1.5	7.3
Only FFN+	52	3.9	5.8	11.5	73	2.7	9.6	19.2
Only CL ≤25 mm	109	3.7	9.2	18.4	64	0	4.7	15.6
Only PSPB	...	...	...	...	278	1.8	8.6	17.6
FFN+ + CL ≤25 mm	17	35.3	58.8	64.7	16	18.8	25.0	43.8
FFN+ + PSPB	...	...	...	...	25	24.0	40.0	48.0
CL ≤ 25 mm + PSPB	...	...	...	...	48	8.3	29.2	35.4
All three	...	...	...	...	10	50.0	60.0	60.0

Notes. FFN+ = fetal fibronectin positive; CL = cervical length; PSPB = prior spontaneous preterm birth.

TABLE 4—Multivariate Logistic Regression Model for Predicting Spontaneous Preterm Birth (SPB)

	SPB <32 Weeks	
	Nulliparas OR (95% CI)	Multiparas OR (95% CI)
Black vs non-Black	2.7 (0.8, 9.3)	0.7 (0.3, 1.6)
BV^+ vs BV^-	1.7 (0.6, 4.8)	2.4 (1.1, 5.6)
FFN^+ vs FFN^-	9.8 (3.5, 27.4)	1.0 (4.4, 23.2)
CL ≤25 mm vs >25 mm	8.7 (3.2, 23.5)	4.6 (1.9, 10.8)
BMI <19.8 vs ≥19.8	1.2 (0.4, 3.6)	1.2 (0.5, 3.0)
Contractions vs none	1.7 (0.5, 5.9)	0.9 (0.3, 2.4)
Vaginal bleeding vs none	2.3 (0.6, 8.7)	2.6 (1.0, 6.8)
Pelvic infection vs none	0.5 (0.1, 1.8)	1.7 (0.7, 3.9)
Prior SPB vs none	— (—)	5.0 (2.2, 11.4)
	SPB <35 Weeks	
	Nulliparas OR (95% CI)	Multiparas OR (95% CI)
Black vs non-Black	1.2 (0.6, 2.6)	1.3 (0.7, 2.2)
BV^+ vs BV^-	0.9 (0.4, 2.0)	1.3 (0.8, 2.2)
FFN^+ vs FFN^-	6.1 (2.7, 13.7)	5.2 (2.9, 9.4)
CL ≤25 mm vs >25 mm	8.9 (4.5, 17.8)	4.1 (2.3, 7.2)
BMI <19.8 vs ≥19.8	1.6 (0.7, 3.3)	1.5 (0.9, 2.6)
Contractions vs none	1.8 (0.7, 4.2)	1.9 (1.1, 3.6)
Vaginal bleeding vs none	1.1 (0.3, 3.4)	1.9 (1.0, 3.6)
Pelvic infection vs none	1.4 (0.7, 3.0)	1.1 (0.7, 1.9)
Prior SPB vs none	— (—)	5.8 (3.5, 9.5)
	SPB <37 Weeks	
	Nulliparas OR (95% CI)	Multiparas OR (95% CI)
Black vs non-Black	1.5 (0.9, 2.5)	1.4 (0.9, 1.9)
BV^+ vs BV^-	1.1 (0.6, 1.8)	1.1 (0.8, 1.6)
FFN^+ vs FFN^-	2.9 (1.5, 5.5)	3.4 (2.1, 5.4)
CL ≤25 mm vs >25 mm	4.6 (2.8, 7.5)	2.5 (1.6, 3.8)
BMI <19.8 vs ≥19.8	2.1 (1.4, 3.4)	1.7 (1.2, 2.5)
Contractions vs none	2.2 (1.3, 3.8)	1.5 (1.0, 2.1)
Vaginal bleeding vs none	1.0 (0.5, 2.1)	1.5 (1.0, 2.4)
Pelvic infection vs none	1.4 (0.9, 2.3)	1.3 (0.9, 1.9)
Prior SPB vs none	— (—)	2.6 (1.9, 3.6)

Note. OR = odds ratio; CI = confidence interval; BV = bacterial vaginosis; CL = cervical length; BMI = body mass index.

more than 50%. Similar findings were present when spontaneous preterm birth was defined as occurring at less than 35 weeks and at less than 37 weeks.

This population, while not selected for specific risk factors, had a majority of Black women and a 10% incidence of spontaneous preterm birth. Therefore, it may not be appropriate to generalize all findings to other populations. For example, bacterial vaginosis was more common in Black women and in them had a population attributable risk of 40% for spontaneous preterm birth at less than 32 weeks. If this result is confirmed, a potentially treatable factor responsible for a substantial portion of the Black–non-Black difference in early spontaneous preterm birth will be identified. Bacterial vaginosis posed no population attributable risk for spontaneous preterm birth at less than 32 weeks in non-Black women, but the reason for this difference is not clear. However, the association between Black race and bacterial vaginosis in this population confirms the relationship observed in the VIP study[24] and elsewhere.[11] Most, but not all, studies find a low body mass index to be a strong risk factor for spontaneous preterm birth. Whether this relationship is due to a specific vitamin or mineral deficiency associated with low caloric consumption or to other factors is unknown.[25] The greater population attributable risk for spontaneous preterm birth associated with a low body mass index in non-Black compared with Black women has also been noted previously.[26] The reason for this difference is also not apparent. We emphasize that the data reported here were collected at 22 to 26 weeks. It would not be appropriate to generalize these results to data collected at other times during pregnancy.

Among our most interesting data was the relationship of a short cervix to the other risk factors, especially prior spontaneous preterm birth. Since we had no data on cervical length prior to 22 to 24 weeks, we could not determine whether a short cervix was present before the pregnancy and was a characteristic of the mother, or if the cervix shortened during pregnancy. Nevertheless, a short cervix and a prior spontaneous preterm birth were strongly associated with one another, and both independently predicted spontaneous preterm birth. The lack of an association between a short cervix and most of the traditional risk factors suggests that a short cervix is a major independent risk factor for spontaneous preterm birth.

Our results suggest that there are several important pathways leading to spontaneous preterm birth. Black race appears to be linked to this outcome predominantly through bacterial vaginosis and fetal fibronectin. A prior spontaneous preterm birth is associated with a subsequent one through a short cervix. With a better understanding of these interactions, we may be able to develop targeted interventions directed at the women with specific risk factors for spontaneous preterm birth. Such an approach will likely be more successful in reducing spontaneous preterm birth than has been achieved with nonspecific interventions.[23] □

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References

1. Wen SW, Goldenberg RL, Cutter G, Hoffman H, Cliver SP. Intrauterine growth retardation and preterm delivery: Prenatal risk factors in an indigent population. *Am J Obstet Gynecol* . 1990;162:213–218.
2. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. *Bull World Health Organ*. 1987; 65:663–737.
3. Berkowitz GS. An epidemiologic study of preterm delivery. *Am J Epidemiol.* 1981;113: 81–92.
4. Eisner V, Brazie JV, Pratt MW, Hexter AC. The risk of low birthweight. *Am J Public Health*. 1979;69:887–893.
5. Fedrick J, Anderson AB. Factors associated with spontaneous pre-term birth. *Br J Obstet Gynaecol.* 1976;83:342–350.
6. Funderburk SJ, Guthrie D, Meldrum D. Suboptimal pregnancy outcome among women with prior abortions and premature births. *Am J Obstet Gynecol.* 1976;126:55–60.
7. Levkoff AH, Westphal M, Miller III MC, Michel Y. Maternal risk factors in infants with very low birth weight. *Am J Obstet Gynecol.* 1982;60:612–616.
8. Meis PJ, Ernest JM, Moore ML. Causes of low birth weight births in public and private patients. *Am J Obstet Gynecol.* 1987;156: 1165–1168.
9. Papiernik E, Kaminski M. Multifactorial study of the risk of prematurity at 32 weeks of gestation, I: a study of the frequency of 30 predictive characteristics. *J Perinat Med.* 1974;2:30–36.
10. Shiono PH, Klebanoff MA, Graubard BI, Berendes HW, Rhoads GG. Birth weight among women of different ethnic groups. *JAMA.* 1986;255:48–52.
11. Hay PE, Lamont RF, Taylor-Robinson D, Morgan DJ, Ison C, Pearson J. Abnormal bacterial colonization of the genital tract and subsequent preterm delivery and late miscarriage. *BMJ.* 1994;308:295–298.
12. Kurki T, Sivonen A, Renkonen O, Savia E, Ylikorkala O. Bacterial vaginosis in early pregnancy and pregnancy outcome. *Obstet Gynecol.* 1992;80:173–177.
13. Hauth JC, Goldenberg RL, Andrews WW, DuBard MB, Copper RL. Treatment with metronidazole and erythromycin reduces preterm delivery in women with bacterial vaginosis. *N Engl J Med.* 1995;333:1732–1736.
14. Meis PJ, Goldenberg RL, Mercer B, et al. The preterm prediction study: significance of vaginal infections. *Am J Obstet Gynecol.* 1995; 173:1231–1235.
15. Goldenberg RL, Iams JD, Mercer BM, Meis PJ, Moawad AH, Copper RL. The preterm prediction study: early fetal fibronectin testing predicts early spontaneous preterm birth. *Obstet Gynecol.* 1996;87:643–648.
16. Lockwood CJ, Wein R, Lapinski R, et al. The presence of cervical and vaginal fetal fibronectin predicts preterm delivery in an inner-city obstetric population. *Am J Obstet Gynecol.* 1993;169:798–804.
17. Lockwood CJ, Senyei AE, Dische MR, et al. Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery. *N Engl J Med.* 1991;325:669–674.
18. Nageotte MP, Casal D, Senyei AE. Fetal fibronectin in patients at increased risk for premature birth. *Am J Obstet Gynecol.* 1994;170:20–25.
19. Iams JD, Casal D, McGregor JA, et al. Fetal fibronectin improves the accuracy of diagnosis of preterm labor. *Am J Obstet Gynecol.* 1995;173:141–145.
20. Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. *N Engl J Med.* 1996;334:567–572.
21. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosis of bacterial vaginosis is improved by a standardized method of Gram stain interpretation. *J Clin Microbiol.* 1991; 29:297–301.
22. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic Research.* New York, NY:Van Nostrand Reinhold; 1982:160–164.
23. Goldenberg RL. The prevention of low birthweight and its sequelae. *Prev Med.* 1994;23: 627–631.
24. Goldenberg RL, Klebanoff MA, Nugent R, Krohn MA, Hillier S, Andrews WW, the VIP Study Group. Bacterial colonization of the vagina during pregnancy in four ethnic groups. *Am J Obstet Gynecol.* 1996;174: 1618–1621.
25. Goldenberg RL, Tamura T, Neggers Y, et al. The effect of zinc supplementation on pregnancy outcome. *JAMA.* 1995;274:463–468.
26. Hickey CA, Cliver SP, McNeal SF, Hoffman HJ, Goldenberg RL. Prenatal weight gain patterns and spontaneous preterm birth among nonobese Black and White women. *Obstet Gynecol.* 1995;85:909–914.